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EDITORIAL COMMENT

Symptoms and Left Ventricular Size and Function in Patients With Chronic Aortic Regurgitation*

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Patients with chronic aortic regurgitation (AR) are generally subject to low morbidity during a long asymptomatic period; many patients, even those with a severe regurgitant lesion, remain asymptomatic for decades. Others, while lacking clear evidence of worsening regurgitation, show evidence of progressive left ventricular (LV) overload and eventually develop symptoms or LV dysfunction. Conventional wisdom holds that the development of cardiac symptoms and/or the development of LV dysfunction can be taken as an indication for surgical correction of the regurgitant lesion (1). In this issue of the *Journal*, Tarasoutchi et al. (2) report their experience with a "symptom-based strategy" in 75 patients with chronic AR. Testing the hypothesis that outcomes achieved with this strategy might better suit the socioeconomic feature of their patient population, they did not rely on changes in LV size or function, but rather waited for the development of symptoms before proceeding with surgery. Their rationale for adopting this approach was to "avoid early exposure to the complications of valve prosthesis."

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On first glance the conclusion of Tarasoutchi et al. (2) appear to be at odds with some of the recommendations published in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with valvular heart disease (1). Their study was prospective with clinical, echocardiographic, and exercise evaluations every 6 to 12 months. At the time of the baseline studies, virtually all patients had LV enlargement and a normal LV ejection fraction (EF). After 10 years, 38 patients remained asymptomatic with relatively minor changes in LV size and function. The other 37 patients developed symptoms (after an average of 4.6 ± 1.0 year) and surgery was then recommended. Aortic valve replacement (AVR) was performed in 34 patients (average 5.9 ± 2.5 years). Three unoperated patients died and there were four late deaths related to prosthetic valve endocarditis, thrombosis, or dysfunction. There were no deaths related to heart failure. Sixty-eight patients (90%) were alive and well at the end of the 10-year study period.

It is important to emphasize that virtually all of the patients in this study had a normal LV EF; only two asymptomatic patients had an EF <50%. Certainly "favorable" outcomes in only two patients cannot be used to support the use of a symptom-based strategy in all patients with a depressed EF. It does appear, however, that substantial LV enlargement did not portend a poor outcome in these relatively young patients with rheumatic valvular disease. With these possible exceptions, the "symptom-based strategy" is consonant with the approach presented in the ACC/AHA guidelines.

LV response. Chronic AR burdens the heart with a volume load that leads to a series of compensatory myocardial and circulatory adjustments (3,4). The major adjustment is enlargement of the ventricle. An increase in end-diastolic volume is crucial because it provides the only sustainable mechanism for generation of a stroke volume large enough to allow a normal systemic blood flow despite a significant regurgitant fraction. Thus, a large end-diastolic volume is a necessary and an expected compensatory adaptation to the regurgitant lesion and in this regard it is similar to that seen in chronic mitral regurgitation (5). Mitral regurgitation, however, produces a relatively pure LV volume overload, while AR produces a combined LV volume and pressure overload with a combination of eccentric and concentric hypertrophy. During the compensated stage of chronic AR, myocardial function may not be entirely normal, but the ventricular EF remains in the normal range and most patients remain asymptomatic for years or even decades.

LV chamber size. Recognizing that ventricular enlargement is an obligatory adjustment to the volume load imposed by chronic AR, the mere presence of a large end-diastolic dimension (EDD) can be considered only a marker of hemodynamically significant AR. The question then arises: at what point can measurements of EDD be useful in managing patients with chronic AR? Certainly modest LV enlargement with normal systolic function carries a benign prognosis (6). The implications of extreme or progressive chamber enlargement are less certain.

Asymptomatic patients with a normal EF but extreme LV enlargement (i.e., EDD >75 mm) is considered a class IIa indication for AVR. This recommendation is based largely on a report of sudden death in two of three patients with an EDD >80 mm (7). However, other reports suggest that extreme LV enlargement may not be so ominous. For example, Klodas et al. (8) analyzed postoperative results in 31 patients with an EDD >80 mm. In this study, the EDD was not predictive of survival, EF, or functional class (FC); severe chamber enlargement in the absence of systolic dysfunction did not preclude a satisfactory clinical outcome. In the Tarasoutchi et al. (2) study, 27 of the 75 patients had

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an EDD >75 mm; 20 patients eventually developed symptoms while 7 patients remained asymptomatic. Despite this degree of enlargement, LV function remained normal and clinical outcome was favorable. These studies do not strongly support the use of extreme LV enlargement as an indication for AVR—unless cardiac symptoms and/or systolic dysfunction are present.

Is a progressive increase in LV chamber size a more cogent indication for AVR? Tarasoutchi et al. (2) found no change in the mean value for EDD between baseline and the final 10-year study in the 38 patients who remained asymptomatic (although EDD increased from <75mm to >75mm in several patients), nor did a change in EDD correspond to the development of symptoms. These observations are similar to those of Bonow et al. (6), who found that EDD did not change significantly between their early and late studies; over an average of 49 months only 15% of their patients exhibited an increase in EDD that was more than 5 mm. Therefore, it appears that the vast majority of patients with chronic severe AR exhibit little or no change in EDD for periods ranging from 4 to 10 years and that the development of LV dysfunction cannot be correlated closely with progressive LV enlargement. Certainly patients exhibiting progressive LV enlargement should be followed closely, but a gradual increase in EDD in an asymptomatic patient with a normal EF is not necessarily an indication for AVR—unless accompanied by cardiac symptoms and/or LV systolic dysfunction.

LV systolic function. Clinical investigators have repeatedly confirmed the importance of LV systolic function as a determinant of clinical outcome in patients with chronic AR. Ejection fraction and the echocardiographic fractional shortening are the most widely used and accepted indices of systolic function. The end-systolic diameter (ESD) is also often used, but it should be recognized that end-systolic size is a function of diastolic chamber size and contractile function; end-systolic volume may increase as a consequence of a larger end-diastolic volume and/or a lower EF. An ESD >55 mm is essentially a surrogate for impaired systolic function because it will be associated with a reduced shortening fraction when the EDD is <80 mm. Since the ESD depends on LV chamber size and systolic function, as well as body size, either the EF or shortening fraction should be superior to the ESD because these parameters are dimensionless and independent of body size (vide infra).

Tarasoutchi et al. (2) report that the majority of their patients had normal systolic function at baseline; the EF was >50% in 72 of the 75 patients. Over the 10-year follow-up period, they found a tendency for EF and shortening fraction to decline in asymptomatic patients; approximately one-third of patients exhibited a progressive increase in ESD, but only one patient in each group showed an abnormal EF that was not present in the baseline study. Likewise, Bonow et al. (6) found a significant decline in EF (>5%) and an increase in ESD in patients who remained stable as well as in those that required AVR. Thus, systolic function, measured by any of the standard techniques, tends to decline in many, but not all, patients with severe AR. These changes are harbingers of the development of symptoms, and can be used to identify patients who may soon require AVR. However, it does not appear that a progressive decline in systolic function should be used as a strong indication for AVR in an asymptomatic patient—unless the EF falls below 50%.

Symptoms. Most published papers and texts indicate that symptoms are an unequivocal indication for AVR, but a careful definition of symptoms is rarely provided. The interpretation of a patient's description of symptoms, however, is often difficult and clinicians are forced to consider the contributions of other medical conditions, such as chronic pulmonary disease, obesity, and especially physical deconditioning, which is a common cause of effort dyspnea and fatigue.

A widely quoted study of patients with chronic severe AR specifically defines symptoms requiring AVR as "overt evidence of LV failure (paroxysmal nocturnal dyspnea, orthopnea, or dyspnea at rest), or dyspnea severe enough to interfere greatly with quality of life" (7). Tarasoutchi et al. (2) were not as specific with their definition of symptoms. Thus, they indicate that they operated on some patients with FC II symptoms, but the discussion suggests that at least some FC II patients were considered to be asymptomatic. In patients with a normal EF, the ACC/AHA guidelines suggest AVR in patients with a normal EF and FC III to IV symptoms, and in patients with a new onset of "mild" dyspnea if there is evidence of increasing LV size and/or decreasing EF (both are class I indications). The development of "mild" symptoms in a patient with a normal EF and stable LV size and function may also be an indication for AVR (a class IIa indication). The problem remains, however, that early symptoms are often difficult to assess. Observations made during exercise may contribute to the evaluation. Ultimately, since symptoms are of signal importance in the management of patients with chronic AR, it behooves the physician to be certain of the cardiac origin of symptoms before recommending AVR.

Age. In virtually all forms of heart disease, age is a strong correlate of clinical outcome. As Tarasoutchi et al. (2) have noted, this is no less true of the course of chronic AR. In their study, the patients that eventually developed symptoms were an average of seven years older than their asymptomatic counterparts. Although the "time of diagnosis" was similar in the two groups it would seem that differences in the duration of the LV volume overload could be a determinant of whether or not symptoms develop. Thus, the patient's age may well be an extenuating factor that should be considered when applying the ACC/AHA guidelines or the "symptom-based strategy."

Anthropometric normalization. Anthropometric normalization of LV volume or internal diameter should be a consideration in any study of LV size and function. Unfortunately, Tarasoutchi et al. (2) did not normalize LV

dimension for body size. Although this would not necessarily have affected their conclusions about symptoms and clinical outcomes, other important correlations might have been obscured. In a study contrasting outcomes of men versus women after surgical correction of chronic AR, Klodas et al. (9) concluded that the unadjusted LV diameter criteria established in men are almost never reached in women. This important observation would seem to support the concept of normalization for body size, but these authors found that "LV dimensions corrected for body surface area (BSA) were not predictive of late survival." By contrast, Dujardin et al. (10) found that ESD normalized for BSA, was a "predictor of outcome." This result is consonant with older studies (11), but it might now be reasonable to question the notion that BSA is appropriate for this purpose. Normalization for BSA tends to mask the diagnosis of LV enlargement, especially in patients who are overweight (12). The use of height and a consideration of gender are likely to be more appropriate than BSA alone (13).

Pharmacologic issues. It has long been recognized that vasoactive drugs have the potential to affect LV size and function in regurgitant lesion of the mitral and aortic valves (14). The hydraulic determinants of the regurgitant volume are well recognized and best understood in the context of the orifice equation. This equation, based on the Torricelli principle, states that flow through as orifice varies by the square root of the pressure gradient across that orifice. Thus, the major determinants of aortic regurgitant volume are the regurgitant orifice area, the duration of diastole, and the diastolic pressure gradient across the valve. In selected patients, vasoactive and other pharmacologic interventions can affect all three of these determinants and should be considered in any study of chronic AR.

Almost one-third of the patients reported by Tarasoutchi et al. (2) received digitalis or diuretics. Presumably these were symptomatic patients, but the authors specifically state that none of the asymptomatic patients were treated with vasodilator drugs. Certainly, no one would argue the use of vasoactive drugs in symptomatic patients, especially those with depressed systolic function (14), but the benefits of such treatment in asymptomatic patients with normal LV function is less well established. One study indicated that the use of nifedipine benefited patients in this category (15). Based on measurements of LV size and function, however, the patients that were treated with nifedipine followed a course that was similar to untreated, low-risk patients as published by others (6,7,16). Those treated with digitalis followed a less favorable course and subsequently a deleterious effect of digitalis was suggested (17). Bonow et al. (7) also reported the development of symptoms in two patients that had been treated with digitalis. We do not use digitalis in asymptomatic, low-risk patients and we generally reserve the use of vasoactive drugs to patients who are not in low-risk groups.

Inhibition of the renin-angiotensin system has been shown to have a salutary cardiac effect in asymptomatic patients with AR (18). Favorable changes in LV volume and mass are widely thought to be a consequence of a decrease in regurgitant volume, but angiotensin-converting enzyme inhibitors also produce a decrease in LV volume in experimental AR without a change in regurgitant volume or regurgitant fraction (19). This can be explained by a systolic unloading effect that results in an increased LV emptying, with little or no change in the diastolic pressure gradient across the aortic valve (vide supra). Therefore, if vasoactive drugs are used in patients with calcific aortic valve disease and a fixed orifice area, the primary target should be systolic hypertension and the goal should be afterload reduction. In patients with aortic root disease, a decrease in aortic distending pressure may be of further benefit by directly affecting the regurgitant orifice area.

Conclusions/Comment. The data reported by Tarasoutchi et al. (2) add to our understanding of the natural history of chronic AR and provide additional insight into our deliberations about the timing of AVR. Their experience confirms a relatively benign natural history of severe AR in asymptomatic patients with normal LV function, despite substantial LV enlargement. In such patients, a favorable outcome can be expected if AVR is postponed until after the development of symptoms. However, their experience with patients who have a low EF was very limited, therefore, their symptom-based strategy should not be extrapolated to patients with a low EF. Indeed, patients with a decreased EF are candidates for AVR whether they are symptomatic or not (a class I indication).

There are clearly circumstances wherein the principle of primum non nocere may supervene when, for example, as noted by Tarsoutchi et al. (2), a high rate of prosthetic valve related complications is anticipated after AVR. In this situation, temporization and vasodilator treatment, particularly in younger patients, may be justifiable.

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